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PATENT #100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit: 1655

Application of Ward et al.

Serial No.: 09/610,935

Filed: July 6, 2000

For: TARGET REAGENTS THAT ENHANCE REACTION-PRODUCT ANALYSIS

Examiner: Bradley L. Sisson

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Amendment B

TECH CENTER 1600/2900

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS

Sir:

In response to the final Office action issued on November 1, 2001 (Paper No. 7) and further to the Interview Summary of February 22, 2002, (Paper No. 8, copy of the summary enclosed herein), please enter the following amendments:

IN THE CLAIMS:

Please amend claims 11, 13, 14, 15, 16, 20, 21, and 22:

C1 11. (amended) A composition comprising a thermostable DNA polymerase for an *ex vivo* polymerase reaction in which a nucleic acid polymer product complementary to a nucleic acid polymer template is prepared, and an anionic tracer dye compatible with the thermostable DNA polymerase, the composition being substantially free of the nucleic acid polymer template and having an optical density greater than about 5 at a visible wavelength of maximal tracer absorbance.

C2 13. The composition of claim 11 having a density of at least about 1.01 g/cm³.

C₂ 14. The composition of claim 11 having a density of at least about 1.1 g/cm³.

15. The composition of claim 11 wherein the optical density of the composition is at least about 15 at a visible wavelength of maximal tracer absorbance.

16. The composition of claim 11 wherein the optical density of the composition is about
5 200 - 400 at a visible wavelength of maximal tracer absorbance.

C₃ 20. The composition of claim 11 wherein the polymerase is Taq polymerase.

21. (amended) The composition of claim 11 wherein the tracer dye is comprised of acid violet 5 and acid red 1.

22. (amended) The composition of claim 14 wherein the optical density of the composition is about 200 - 400 at a visible wavelength of maximal tracer absorbance, the polymerase is a Taq polymerase, and the tracer dye consists of 20% acid violet 5 and 80% acid red 1.

Please cancel claims 1-10, 12, 17, 18, 19, and 34-41.

REMARKS

Upon entry of the amendment, claims 11, 13-16, and 20-22 are pending in the application. Support for the amendment to claim 11 can be found in claims 12, 18, and 19.

Reconsideration is requested of the rejection of claims 1-22 and 34-41 under 35 U.S.C. §112, first paragraph, on the asserted basis that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed invention at the time the application was filed.

Although it is maintained that the invention defined by claims 1-10 and 34-41 meet the written description requirement of 35 U.S.C. §112, first paragraph, for the reasons stated in Applicants' Response Under 37 C.F.R. 1.111 (Paper No. 6), filed on August 1, 2001, this portion of the rejection is presently moot in view of the cancellation of these claims. Applicants, however, reserve the right to pursue the canceled subject matter in its full scope in a continuation application. As to the remaining subject matter, *i.e.*, claims 11, 13-16, and 19-22, as amended, Applicants request reconsideration.

"Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 2002 WL 1540815 at *4 (Fed. Cir. 2002)(citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)). The standard is whether the description allows persons of ordinary skill in the art to recognize that the inventor had possession of the claimed invention at the time of filing. *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996); *see also, Vas-Cath*, 935 F.2d at 1557. Moreover, there is a strong presumption that an adequate written description of the claimed invention is present in the originally filed claims, *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976), and therefore, the PTO has the initial burden of demonstrating why a person of ordinary skill in the art would not recognize in the disclosure a description of the invention defined by the claims. *Id.* at 263. Consequently, rejection of an original claim for lack of written description *should be rare*. "Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, 'Written Description Requirement'" 66 Fed. Reg. 1099 (Jan. 5, 2001)(emphasis added; hereinafter "Guidelines").

In this case, the specification contains *ipsis verbis* support for the currently pending claims. In a preferred embodiment, the composition of the present invention comprises a thermostable DNA polymerase¹ and an anionic tracer dye.² Example 1 further describes a composition comprising a particular thermostable polymerase, Taq polymerase, and a mixture of

¹Specification at page 12, lines 7-8.

²Specification at page 13, lines 21-22.

two anionic tracer dyes, acid violet 5 (20%) and acid red 1 (80%). As such, Example 1 conveys to one of ordinary skill that Applicants were in possession of a composition defined by claim 11.

As demonstrated by the Declaration under 37 C.F.R. 1.132 of Brian W. Ward ("Ward Declaration"), attached hereto as Exhibit A, and the references disclosed therein, attached hereto as Exhibit C, the structural and functional characteristics of Taq polymerase are common and conserved among other thermostable polymerases. These similarities are readily appreciated and understood by those of ordinary skill in the art, as the structure and function of polymerases are well understood in the art. *See*, Ward Declaration, paragraphs 1-19. As such, a person of ordinary skill would understand that other thermostable DNA polymerases could be substituted in place of Taq polymerase in the composition of Example 1 to form other compositions of claim 11 for the following reasons:

- Most DNA polymerases possess various common structural and functional characteristics that are highly conserved even among unrelated polymerases.³
- The presence of these common structural and functional characteristics create a rather unvarying overall structure among DNA polymerases. This likewise causes DNA polymerases to share a substantially uniform mechanism of action.⁴
- The common structure of DNA polymerases resembles a half-open right hand, comprising a palm, fingers, and thumb subdomains. This structure is by far the most prominent feature common to all known polymerases.⁵
- Despite some differences in the amino acid sequences and structures of polymerases from different families, features essential for polymerase activity are highly conserved.⁶
- Polymerases display a common reaction mechanism. This mechanism, as well as the geometry of the active site, are highly conserved among polymerases.⁷

³Ward Declaration at ¶ 9.

⁴Ward Declaration at ¶ 9

⁵Ward Declaration at ¶ 10.

⁶Ward Declaration at ¶ 10.

⁷Ward Declaration at ¶¶ 13 and 17.

- The reaction mechanism, as well as the geometry of the reaction site, are highly conserved.

Stated another way, a person of ordinary skill would understand that the possession of Taq polymerase in one composition falling within the scope of claim 11 reflects possession of all thermostable DNA polymerases in other compositions falling within the scope of claim 11 in view of the common structural, functional, and behavioral characteristics of thermostable DNA polymerases.

Likewise, the exemplification of several anionic tracer dyes in Example 1 is sufficient to meet the written description requirements of 35 U.S.C. 112, first paragraph, with respect to the anionic tracer dye requirement for the composition of claim 11. A person of ordinary skill would understand that other anionic dyes could be substituted in place of the six dyes used in the composition of Example 1 to form other compositions of claim 11 for the following reasons:

- Anionic dyes were selected because of the minimal likelihood of interacting with the nucleic acids during the polymerization. Specifically, since the nucleic acid products of PCR are highly anionic, and thereby traverse an agarose gel in a particular direction, it is preferable that the tracer dye be anionic as well for the same reason.⁸
- The list of anionic dyes was furthered focused on the basis of characteristics such as ethanol precipitation, solid phase extraction, PCR toxicity, and ligation/transformation toxicity for use in the particular embodiment of Example 1. However, based upon the structural and functional characteristics of Taq polymerase and the knowledge and skill of those in the art, it is clear that other anionic dyes would work as well.⁹
- The characteristics of the specific dyes disclosed are indicative of the characteristics of other dyes that could be used with equally satisfactory results.¹⁰

As described in Example 1, there are numerous dyes that are compatible with Taq polymerase and the six dyes demonstrated in Example 1 are merely six *exemplar* dyes of one *particular* embodiment of the invention. As described in greater detail in Example 1, only red dyes were

⁸Ward Declaration at ¶ 21.

⁹Ward Declaration at ¶ 24.

¹⁰Ward Declaration at ¶ 27.

considered for evaluation in that Example, but **not** because the other colors would not work with the polymerase. **The color red was selected for aesthetic reasons only and confers no particular advantage as a tracer.**¹¹ Thus, other anionic dyes of other colors which could have been selected instead of, or in addition to, the red dyes selected were arbitrarily excluded for reasons of aesthetics.

Figure 5 recites and Figure 6 illustrates the steps taken to select a red anionic dye in Example 1. From 180+ red dyes (absorbance max between 450 and 570 nm) (Table 1), approximately 40 anionic red dyes were selected (Table 2). Of these, the ones which were deemed too yellow or purple, again for purely aesthetic reasons, were eliminated from consideration. The remainder of the approximately 40 were then evaluated for other characteristics such as ethanol precipitation, solid phase extraction, PCR toxicity, and ligation/transformation toxicity.¹² This evaluation yielded six red anionic tracer dyes which were found to be substantially equivalent as tracer candidates.¹³ Of these, two were selected for aesthetic reasons.¹⁴

If the dye selection procedure described in Example 1 illustrates anything, it illustrates that many anionic dyes can be used in the composition of claim 11. Otherwise, aesthetics would not have been a criteria and certainly would not have been the first criterion. Stated another way, if the universe of anionic dyes were limited, all anionic dyes which impart a color other than a particular, arbitrarily selected shade of red would not have been excluded from consideration **before** they were evaluated for performance characteristics (as was done in Example 1). A person of ordinary skill would understand from Example 1, therefore, that compositions of claim

¹¹Specification, at page 18, lines 19-20. The desired color was a particular shade of red which is commonly associated in the field with Applicant's assignee, Sigma-Aldrich Company. Ward Declaration at ¶ 22.

¹²Specification, at page 26, line 5 to page 28, line 12.

¹³Specification at page 27, lines 1-3.

¹⁴Specification at page 28, lines 20-22; Ward Declaration at ¶ 22. See also, Figures 5 and

11 comprising anionic dyes of any of a wide variety of colors and shades may be arbitrarily obtained by a selection process comparable to that of Example 1.

A specification need not exemplify *all* possible combinations or embodiments of the invention; rather, it is sufficient to describe and enable representative embodiments of the invention. The written description requirement may be met for a claimed genus by a sufficient description of a "representative number of species." *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). *See also, Enzo Biochem, Inc.*, 2002 WL 1540813 at *7. Furthermore,

[a] "representative number of species" means that the species which are adequately described are representative of the entire genus. . . . [T]here may be situations where one species adequately supports a genus [citing, *Rasmussen*, 650 F.2d 1212, 1214 (C.C.P.A. 1981); *In re Herschler*, 591 F.3d 693, 697 (C.C.P.A. 1979); *In re Smythe*, 480 F.2d 1376, 1383 (C.C.P.A. 1973); cf. *Tronzo v. Biomet*, 156 F.3d 1154, 1159 (Fed. Cir. 1998)]. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. . . . Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.

66 Fed. Reg. at 1106.

The present specification satisfies the criteria set forth in the Guidelines and case law with respect to the invention defined by claim 11. The skill and knowledge regarding thermostable DNA polymerases is relatively high, the structural and functional characteristics of DNA polymerases are well known, and it is common knowledge that these structural and functional characteristics are conserved as among the various thermostable DNA polymerases. Such characteristics are even conserved as among completely unrelated polymerases.¹⁵

Additionally, as indicated by the Ward Declaration, the dyes of Example 1 are representative of numerous other dyes that could be used in other embodiments of the present

¹⁵See, Ward Declaration, ¶¶ 8-19.

invention with equal success.¹⁶ Specifically, one of skill in the art would readily recognize from the disclosure of Example 1 that the tracer dye could be any dye that is anionic and that does not interfere with the polymerase reaction. As evidenced by the Ward declaration, it follows that the description and demonstration of the Taq polymerase and acid violet 5/acid red 1 embodiment of the invention qualifies as "a representative number of species" of the claimed genus, thereby providing a written description of the genus sufficient to meet the written description requirements of 35 U.S.C. § 112, first paragraph.

In support of its rejection, the Office has cited *In re Shokal*, 113 USPQ 283, 285 (C.C.P.A. 1957) for the proposition that "[it] appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim." The *Shokal* court, however, also noted that "such number will vary, depending on the circumstances of particular cases." In this case, as demonstrated by the Ward Declaration and the references cited therein, the present application is a "particular case" wherein a single thermostable DNA polymerase and multiple anionic dye species provide a sufficient written description to support claim 11. The species disclosed in Example 1 clearly describe the characteristics of both the polymerase and tracer dye components of the claimed composition such that one of ordinary skill in the art would recognize that Applicants were in possession of the "necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." 66 Fed. Reg. at 1106.

The remaining claims depend from claim 11 and impose additional requirements. Claim 20, for example, requires that the polymerase of claim 11 be Taq polymerase. Claim 22, for example, requires that the polymerase be Taq polymerase and that the tracer dye consists of 20% acid violet 5 and 80% acid red 1. The Office cannot seriously maintain that the inventors were not in possession of the invention defined by these claims.

¹⁶See, Ward Declaration, ¶¶ 20-27.